REMARKS

Reconsideration of the application is respectfully requested in view of the following remarks.

I. BASIS FOR AMENDMENTS

The amendments find support throughout the application as filed, including at pages 2-4 and original claim 4. New claim 82 finds support, e.g., at page 6 of the application, and its dependent claims are similar to other existing dependent claims.

II. RESTRICTION REQUIREMENT AND ELECTION

Applicants confirm the provisional election as set forth at page 5 of the Action, with traverse.

The Office alleged lack of unity and divided the claims into three restriction groups. A "special technical feature" that unifies the three restriction groups relates to the role/association of elevated Prox-1 expression in colon cancer. The Office alleges that Parr et al. (2003) is evidence that the role of Prox-1 in cell proliferation was known in the art at the time the invention was made, and alleges that, therefore, unity is lacking. However, Parr (2003) is not evidence that anything was known at the time the invention was made because the Applicants have antedated Parr et al. with a Rule 131 declaration filed herewith. This declaration demonstrates that the Applicants invented before Parr (2003) was published. Thus, unity of invention exists, and the restriction requirement should be withdrawn.

Additionally, claim 15 is a linking claim that links Groups 1 and 2. Even if the restriction is maintained, Group 2 claims should be rejoined with an allowable claim 15. See MPEP § 809 ("[S]hould any linking claim be allowable, the restriction requirement between the linked inventions must be withdrawn. Any claim(s) directed to the non-elected invention(s), previously withdrawn from consideration, which depends from or requires all the limitation of the allowable linking claim must be rejoined ....")

III. THE REJECTIONS BASED ON PRIOR ART SHOULD BE WITHDRAWN.

The Office rejected various claims as allegedly anticipated by, or rendered obvious by, Parr et al. (2003), alone or in combination with other references. Submitted herewith is a Rule 131 declaration establishing that the inventors invented the invention before the publication date of Parr et al. (alleged to be publicly available as of 7/17/2003). Because the primary reference is not citable as statutory prior art, the rejections should be withdrawn.

The Rule 131 declaration identifies two documents that were communicated to Marshall Gerstein & Borun (an intellectual property law firm in Chicago IL) before the July 2003 publication date of Parr et al. The undersigned attorney is an attorney at Marshall Gerstein & Borun and was an attorney at Marshall Gerstein & Borun during the relevant time period, and confirms that these documents were received and reviewed at Marshall Gerstein & Borun prior to July, 2003.

IV. THE REJECTION ALLEGING INDEFINITENESS SHOULD BE WITHDRAWN.

The Office alleged that claims 1-15 and 79 were "unclear over the stated purpose of the claimed methods as 'screening colon tissue for a pathological condition' as stated in the preamble of claim 1." The Applicants dispute that there is anything unclear about the original preamble, but have amended the claims to specify in the preamble and the steps that the method relates to screening for colon cancer.

The Office further noted that there is no required method step wherein an 'elevated Prox-1 expression or activity' is in fact detected. The introduction of a "screening" step in amended claim 1 addresses the concern about nexus between the recited purpose and the steps. A screening step matches the preamble and is more appropriate than a step about detecting elevated Prox-1, because "elevated" is only one possible result that would be detected. (A screening assay can provide valuable information where no elevation of Prox-1 is detected too.) For these reasons, the rejection is moot, and should be withdrawn.

The Office also rejected claims 11-13 as unclear. Both the original and currently amended versions of these claims make clear that at least two parameters are measured and used for screening for colon cancer. These are dependent claims and have additional limitations relative to claim 1, which focuses on Prox-1. Thus, these claims are clear, and these rejections should be withdrawn.

V. THE REJECTION ALLEGING LACK OF ENABLEMENT SHOULD BE WITHDRAWN.

The Office alleged a variety of reasons why the Office believed the full scope of the claims was not enabled. The Applicants respectfully traverse.

The Office first alleged lack of enabling disclosure with respect to "methods as claimed which encompass any level of elevated expression or activity." The Applicants respectfully disagree. The specification enables screening based on both elevated Prox-1, and measurements that are not scored as elevated. Absence of elevated Prox-1 is not scored as positive for colon cancer. The observations reported in the specification about the correlation between elevated Prox-1 and colon cancer are statistically significant (specification at p. 60; $p < 0.005$), and the observations reported independently by Parr (2003) also were reported as statistically significant (Parr at p. 536, $p<0.05$). Moreover, in view of the teachings in the specification, routine statistical analysis can be used to provide information about the power/sensitivity/specificity of the prediction made according to the screen. (See, e.g., specification at pp. 5-6.) Based on the teachings in the application, it is within the level of ordinary skill, using only routine procedures, to measure Prox-1 expression or activity in colon tissue and draw a conclusion as to the presence, or absence, of colon cancer based on the measurement. It is understood in the field that such diagnostic/screening tests have a predictive value that can be expressed statistically, depending on the actual measurement. The application describes how to establish a database of measurements to optimize the statistical power of the screening assay. (See, e.g., pp. 5.-6.)

The Office alleged lack of enablement with respect to "any pathological condition." The amended claims specify colon cancer, rendering moot this rejection.

The Office alleged that the specification does not provide any evidence that the elevated Prox-1 mRNA correlates with elevated Prox-1 protein. It is well known that cells translate mRNA to make protein. Also, the specification describes experiments involving siRNA inhibition of Prox-1, which resulted in a suppression of malignant traits of a Prox-1 over-expressing tumor cell line. This data that gene suppression correlated with phenotype change provides indirect evidence that the elevated mRNA is not an artifact, but rather, is indicative of increased Prox-1 protein and Prox-1 protein activity in the affected cells. The data is further supported by analysis of pathways by which Prox-1 may be exerting its effects in these cells. In contrast to the evidence in the application, the Office has failed to provide sound reasoning or evidence as to why elevated Prox-1 mRNA would not also correlate with elevated Prox-1 protein. The Office cites Chen (2002), but the Chen study is not probative because Chen was not looking at the type of phenomena involved in the invention. Chen studied correlations between mRNA level and protein level in 98 *different genes* in adenocarcinomas. Chen did NOT report on whether particular protein levels are increased *in tumor samples compared to normal controls, with respect to genes for which mRNA levels were observed to be increased in tumor samples compared to normal controls.* Thus, the speculation about gene versus protein expression does not support a rejection.

The Office questioned whether the results in the application based on human studies could be extrapolated to other mammals. It should be noted that Example 13 in the application observed elevated Prox-1 in colon cancer from one of two mouse models that were studied. This information is more probative than the articles cites in the Office action, neither of which purported to look at expression or activity of a particular gene in a cancer tissue compared to healthy control tissue.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

VI. CONCLUSION

For the foregoing reasons, the application is believed to be in condition for allowance. If any fees necessary for entry of this response are unpaid, the Office is authorized to charge Deposit Account No. 13-2855 under Order No. 28113/39467A. The Examiner is invited to telephone the undersigned attorney if a telephone conference would expedite prosecution.

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Respectfully submitted,

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